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ST. JAMES'S HOSPITAL • DUBLIN 8
TEL 01-4730589 or 1850-727-727 • FAX 01-4730596 • www.nmic.ie

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ASTHMA

SUMMARY

- **Asthma is the second most prevalent respiratory condition in Ireland.**
- **Inhaled short-acting ß$_2$-agonists on a PRN basis and regular inhaled low-dose corticosteroids are the cornerstone of management.**
- **Educating patients in the correct inhaler technique and reinforcing that technique is crucial for attaining and improving asthma control.**
- **Poor compliance with treatment (inhaler technique and the taking of medication) continues to be a cause of poor asthma control.**

INTRODUCTION

In Ireland, respiratory diseases form the third commonest long-term illness group after cardiovascular and musculoskeletal diseases, with asthma being the second most prevalent single condition reported.[1] The asthma population in Ireland is estimated to be 400,000 (Asthma Society of Ireland), with approximately 5% of the adult population indicating that they have at some point suffered from the condition.[1,2] A morbidity project carried out in the South Eastern Health Board area reported that 6.4% of practice patients had asthma.[3] An Irish Pharmaceutical Health Care Association (IPHA) report in 1997 estimated that 600,000 GP consultations that year were for asthma.[1] This bulletin will deal with the management of asthma in the adult population and children over 12 years of age; a subsequent bulletin will review the management in the younger population.

AETIOLOGY AND NATURAL HISTORY

Asthma can present at any age, but the incidence is highest in childhood. In adults it tends to persist for life and is associated with an accelerated decline in lung function.[4,5,6] Most people with asthma are atopic; exposure to certain stimuli initiates inflammation and structural changes in airways, causing airway hyper-responsiveness and variable airflow obstruction. Common triggers are allergens, upper respiratory tract infections, exercise, changes in temperature and humidity and occupational sensitising agents.[4] Drugs that may trigger symptoms include aspirin, NSAIDs and ß-blockers. Mild asthma in general carries a good prognosis, with progression to severe disease rare. Of patients with severe disease, a small percentage (<5%) respond poorly to therapy and these patients are most at risk of morbidity and death from asthma.[4]

DIAGNOSIS

Asthma is a clinical diagnosis. While there is no standard definition, the International Consensus Report describes asthma as ***a chronic inflammatory disorder of the airways…in susceptible individuals; inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible, either spontaneously or with treatment.***[7] There is no confirmatory diagnostic blood test, radiographic or histopathological investigation. The diagnosis may be corroborated by objective evidence of variable airflow obstruction.
Common symptoms, which are nonspecific, include wheeze, shortness of breath, chest tightness and cough. These symptoms tend to be variable, intermittent, worse at night and provoked by triggers. Information that contributes towards a diagnosis includes a personal or family history of asthma or other atopic conditions (eczema, allergic rhinitis) and a worsening of symptoms after exposure to recognised triggers (pollens, dust, feathered / furry animals, exercise, viral infections, chemicals and tobacco smoke).
Common signs, also nonspecific, include wheeze and reduced lung function. Airway obstruction produces a decrease in peak expiratory flow (PEF) and forced expiratory volume in one-second (FEV_1). Both of these measurements may be normal between episodes of bronchospasm, but are usually lowered when symptoms are present.
Variability of PEF and FEV_1, either spontaneously over time or in response to therapy, is a characteristic feature of asthma. Methods of measuring variable airflow limitation are outlined in Table 1. In older patients, distinguishing chronic severe asthma from chronic obstructive pulmonary disease may be difficult; this is dealt with in a recent NMIC bulletin (Volume 10, Number 3, 2004).

Table 1. Objective measurements which assist a diagnosis of asthma[7]

- > 20% diurnal variation* on ≥ 3 days in a week for two weeks on PEF diary
  or FEV_1 ≥ 15% (or 200ml) increase after short acting ß$_2$ agonist
  or FEV_1 ≥ 15% (or 200ml) increase after trial of steroid tablets (prednisolone 30mg/day for 2 weeks)
  or FEV_1 ≥ 15% decrease after six minutes of exercise (running)
- Histamine or Methacholine challenge in difficult cases

*Diurnal variation is calculated from the formula: [(highest PEF – lowest PEF) ÷ highest PEF] x 100
If using PEF measurements, equivalent changes are 20% from baseline and at least 60 l/min

MANAGEMENT OF STABLE DISEASE

The aims of asthma management are to **control the symptoms** (daytime, nocturnal and exercise-related), prevent acute attacks and achieve the best possible lung function with the minimum of side effects.

Non-Pharmacological Management

Asthmatics should be advised strongly **not to smoke** and **to lose weight**.[8] **Allergen avoidance** measures may be helpful in sensitised individuals, but supporting evidence that they reduce morbidity is tenuous and controversial. A number of studies, including two Cochrane reviews, on **house dust mite control measures** have been published.[9,10] Physical and chemical dust mite reduction methods which has been assessed include complete barrier bed-covering system, removal of carpets, removal of soft toys from bed, high temperature washing of bed linen and dehumidification. To date, these methods have not been found to be of benefit.[9,10] Many experts feel that **removal of pets** from the homes of asthmatic individuals should be recommended, even though observational studies have not found this to be of benefit.[7] **Complementary therapies** that are used by asthma sufferers include herbal and traditional Chinese medicines, acupuncture, homeopathy, hypnosis, massage therapy, breathing exercises and the consumption of fish oils and fatty acids. To date there is insufficient or no evidence of their clinical benefit.[7]

Pharmacological Management

Practical Advice: A stepwise approach as per the updated 2004 British Thoracic Society Guidelines on Asthma Management is outlined in Table 2. The symptoms experienced are correlated with the medication required to achieve symptom control. Patients start therapy at the step most appropriate to the severity of their symptoms. The traditional view of "reliever medication" (i.e. on a PRN basis) and "preventer medication" (i.e. on a regular basis), administered by inhalation continues. All doses of inhaled steroids in this section refer to beclometasone given by a metered dose inhaler.

Non-compliance rates of up to 70% have being documented in a number of studies.[2,5] Poor compliance with treatment (technique and the taking of medication) continues to be a cause of poor asthma control.[2,4]

Table 2. Summary of management of stable asthma[7]

Step 1 **Mild Intermittent Asthma**	**Inhaled short-acting ß$_2$-agonist PRN**
Step 2 **Regular inhaled therapy***	**Regular inhaled corticosteroid** Start at dose appropriate to severity of disease
Step 3 **Add-on therapy***	**Add inhaled long-acting ß$_2$-agonist (LABA)** If good response – Continue LABA If benefit, but control still inadequate – Continue LABA and increase inhaled steroid dose to 800mcg/day If no response – Stop LABA, increase inhaled steroids to 800mcg/day. Consider trial of agents in Step 4
Step 4 **Persistent poor control***	Trial of a) Increasing **steroid dose to 2000mcg/day** or b) Addition of 4th drug – leukotriene receptor antagonist, theophylline, slow release ß$_2$-agonist tablets
Step 5 **Continuous/frequent use of oral steroids***	**Use lowest possible dose** Maintain inhaled steroid at 2000mcg/day Refer for specialist opinion
Before alternating between steps, optimising ***compliance*** *with existing therapies, inhaler technique and the elimination of trigger factors should always be done.* **Inhaled short-acting ß$_2$-agonists PRN are necessary for all steps for the relief of acute symptoms.*	

Step 1 is mild intermittent asthma and involves the use of **inhaled short-acting ß$_2$-agonists (SABA) on a PRN basis** (e.g. salbutamol, terbutaline). Greater benefit has not been documented with regular use compared to as required use.[11] Alternative short-acting bronchodilators include inhaled ipratropium bromide, oral ß$_2$-agonists or oral theophyllines. Excessive use of SABAs has been associated with asthma deaths.[2,7]

Practical Advice: SABAs work quickly with few side effects.

Step 2 patients are those who a) *use SABA > three times a week,* b) *have symptoms > three times a week,* c) *wake at least once a night* or d) *have a history of an acute attack within the past two years*. **Inhaled corticosteroids,** as regular "preventer therapy", are the treatment of choice and have been shown to reduce symptoms, exacerbations, hospital readmissions and asthma deaths.[5,7,12-15] Beclometasone and budesonide are equivalent, while fluticasone provides equal activity at half the dose.[7]

Practical Advice: The majority of patients require < 400mcg/day to achieve maximum or near maximum benefit with ***minimum risk of long-term adverse effects.*** Common side effects are dysphonia and oral candidiasis, which may be reduced by advising patients to rinse out their mouth after inhaling their steroids. Patients taking inhaled steroids should use a spacer device (see below). Once daily dosing (within product licence) with the lowest effective dose may be considered, when good control is established.

Step 3 for those not controlled on step 2 is **add-on therapy**. First choice add-ons are the inhaled long-acting **ß$_2$-agonists (LABA)** salmeterol or formoterol.[16-18] These agents provide bronchodilation for at least 12 hours, with formoterol having a more rapid onset of action.[19] *If there is a response to LABA therapy, but control remains poor,* the LABA should be continued and the dose of inhaled steroid increased to 800mcg/day. *If there is no response,* the LABA should be discontinued and the inhaled steroid should be increased to 800mcg/day. *Sequential add-on therapies, if control is still inadequate* (following LABA and higher doses of inhaled steroid), include leukotriene receptor antagonists (LRA), theophyllines and slow release ß$_2$-agonist tablets. These therapies are associated with improvements in lung function, respiratory symptoms and a reduction in exacerbation rates. The latter two agents are limited by their side-effect profile. Other agents that have been studied include: chromones (cromoglicate and nedocromil), which are of marginal benefit, and short-acting anticholinergics, which have been found to be of no value.
Practical Advice: Start with a LABA. The administration of inhaled steroids and LABAs in separate inhalers is as effective as their administration in combination (e.g. *Seretide®*, *Symbicort®*).

Step 4 for asthmatics with poor control, already on 800mcg/day inhaled steroid + a LABA is **the addition of a fourth drug.** The choices are: a) increase the inhaled steroid to 2000mcg/day, add b) an LRA, c) theophylline or d) slow release ß$_2$-agonist tablets.
Practical Advice: There are no clinical trials indicating which is the best option. Long-term high dose inhaled corticosteroid use has been linked with such systemic effects as reduced bone mineral density, cataract formation and glaucoma.[4,7] High levels of comorbidity (oesophageal reflux, upper airways disease and psychiatric morbidity) have been documented in poorly controlled asthmatics, and patients should be evaluated for the presence of these.[20]

Step 5 is the use of **oral steroids,** either continuously (>3months) or frequently (3-4 per year). Inhaled steroids, at doses of up to 2000mcg/day, are the most effective way of reducing the requirement for long-term oral steroids. The use of other immunosuppressants (methotrexate, ciclosporin, oral gold) in these difficult cases has been studied, and are associated with significant side effects.
Practical Advice: Potential complications of oral steroid use include hypertension, diabetes and osteoporosis.

When can therapy be reduced? Once control is achieved and sustained, gradual stepping down of therapy is recommended.[7] Good control is reflected by the absence of nocturnal symptoms, no symptoms on exercise and the use of SABA less than three times a week. Patients should be maintained on the lowest effective dose of inhaled steroids, with reductions of 25-50% being considered every three months.
Inhaler devices - Patient Education on the correct technique of inhaler use and reinforcing that technique is crucial for attaining and improving asthma control. Choice of inhaler is based on patient preference and assessment of correct use. Spacer devices in combination with metered dose inhalers (MDI) have a number of advantages: a) no need to co-ordinate inhaler activation with inspiration, b) improvement in lung deposition and c) reduction in oropharyngeal deposition (resulting in fewer local side effects and lower systemic absorption).[2] *When a spacer device is being used, only one actuation of the MDI must occur at a time.* There is no clinical difference in the effectiveness of a MDI ± spacer versus a dry powder inhaler (DPI - turbohaler, diskhaler).[7] An exception is budesonide via turbohaler which has been shown to be as effective as twice the same dose administered by MDI + spacer.[2,7] Nebulisers have not been shown to be superior to MDI + spacer for delivery of inhaled steroids in chronic asthma.[2,7]

MANAGEMENT OF ACUTE ASTHMA

Asthma exacerbations are subdivided according to severity, as outlined in Table 3. Acute attacks need rapid, accurate and repeated assessment. The severity of attacks tends to be underestimated.[4] Patients with features of acute severe, brittle or life threatening asthma should be referred to hospital immediately, their managment is outside the scope of this bulletin.

Table 3. Levels of severity of acute asthma exacerbations[7]

Moderate asthma attack	Increasing symptoms PEF > 50-70% best / predicted No features of acute severe asthma
Acute severe asthma	Any one of: PEF 33 – 50% best / predicted RR ≥ 25 / minute HR ≥110 / minute Inability to complete sentences in one breath
Brittle asthma	**Type 1:** Wide PEF variability (> 40% diurnal variation) despite intense therapy **Type 2:** Sudden severe attacks on a background of apparently well controlled asthma
Life threatening asthma	Any one of the following: PEF < 33% best / predicted SpO_2 < 92% PaO_2 < 8 kPa Normal $PaCO_2$ Silent chest Cyanosis Feeble respiratory effort Bradycardia Dysrhythmia Hypotension Exhaustion Confusion Coma

Asthmatics should have an agreed written action plan, and should know when and how to increase their medication and when to seek medical assistance. Patients with a **moderate asthma attack** should ***increase their SABA*** – 2 puffs every 2 minutes up to 10 puffs. If using a spacer device, the puffs should be administered by repeated, *separate*, activations of the MDI. Alternatively administration of salbutamol 2.5-5mg or terbutaline 5-10mg by nebulisation is also effective. ***Oral steroids*** reduce mortality, relapses, subsequent hospital admission and $ß_2$-agonist requirements, and are as effective as parenteral steroids (as long as they are swallowed and retained). Prednisolone 40-50 mg daily is given for at least 5 days or until recovery. Patients need to be advised that doubling the dose of inhaled steroids does not result in double the effect.[21] Patients should be reviewed regularly, and if there is a poor response to these measures or any evidence of deterioration, referral for admission should be sought. Once recovery from the acute attack has occurred, steroid tablets can be stopped abruptly with no need for tapering, provided the patient receives inhaled steroids. ***Routine antibiotic use is not indicated*** for acute asthma.
Following any asthma attack, time should be taken to review the patient's inhaler technique, PEF record keeping and their symptom-based action plan.

ASTHMA DEATHS

There were 92 asthma-related deaths in Ireland in 1999.[1] In the UK, there is a peak of asthma deaths in July and August among younger people (< 44 years) and in December and January in older people. Underestimating the severity of the fatal attack by the doctor, patient or relatives has been identified as a problem.[7,22] Patients at risk of death are those who have severe asthma, are obese, have a history of non-compliance with therapy and have one or more adverse psychological factors such as: alcohol or drug use, employment or income problems, social isolation, childhood abuse or current or recent tranquilliser use. Patients who have had near fatal or brittle asthma should be under specialist supervision on an ongoing basis.

OTHER AREAS

Exercise-induced asthma may occur in all asthmatics and for many is a reflection of poor disease control. Inhaled SABAs should be used prior to exercise and are the agents of choice. Other agents - inhaled steroids, LABAs, theophyllines, LRAs, chromones and oral $ß_2$-agonist also give protection. Anticholinergics, ketotifen or antihistamines are not of benefit.
Occupational asthma is the commonest industrial lung disease in the developed world and accounts for up to 10% of adult-onset asthma. It is preventable but can lead to irreversible airway obstruction if the patient is not removed from the sensitising or irritant agent.[4]
Rhinosinusitis with postnasal drip commonly co-exists with asthma, and is treated with intranasal steroids.
Gastro-oesophageal reflux disease may co-exist and should be treated appropriately.

CONCLUSIONS

Patients need to be more actively involved with their illness and its management in order for compliance to be improved. Proactive structured reviews of asthmatics' care plans are associated with a reduction in exacerbation rates and days lost from normal activity. Compliance with prescribed medications, inhaler technique and treatment plan should be assessed at every opportunity with asthmatic patients.

Table 4. GMS cost of commonly prescribed preparations (cost per inhaler, October 2004)[23]

Name, Strength	Cost €
Salbutamol MDI 100mcg (Ventamol®)	3.30
Terbutaline MDI (Bricanyl®)	7.24
Beclometasone (Beclazone 100®)	12.16
Budenoside DPI–turbohaler 100mcg (Pulmicort®)	23.96
Fluticasone 50mcg MDI (Flixotide®)	9.64
Salmeterol MDI 25mcg (Serevent®)	32.76
Formoterol MDI 12mcg (Oxis®)	29.60
Seretide® MDI 125mcg (Fluticasone 125 + Salmeterol 25)	52.59
Symbicort® turbohaler 200/6mcg (Budesonide 200 + Formoterol 6)	54.59

References available on request. Date prepared: November 2004

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the drug data sheet or summary of product characteristics (SPC), also available on www.medicines.ie for specific information on drug use.

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